TABLET FORMULATION DESIGN

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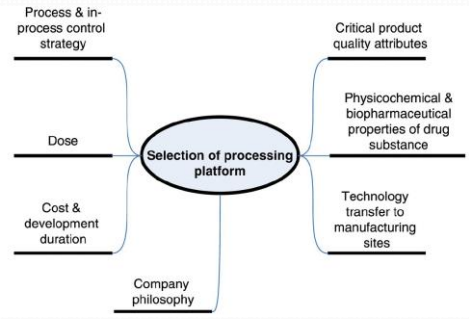
Tablet Formulation Design

Formulation design strategy is decided → **The process of preparing and screening initial formulation possibilities begins**

- **The Goal**:
  to develop a "robust" formulation
  - This objective facilitates identification of the factors that influence the selection of a design process



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Tablet Formulation Design

- **First major design criterion: nature of the API** and in particular the **possible dosage level** (described in Preformulation report and TPP).
- The knowledge of **biopharmaceutical class** to which the API belongs helps in deciding the formulation rationale.
  - In particular, the implications of **low permeability** and **low solubility** must be carefully considered prior to the selection of the processing platform.
- ***For example***, a *poorly soluble drug* often tends to be *poorly wettable*, too. If the **objective** is to obtain a ***fast-dissolving and dispersing dosage form***, inclusion of a **wetting agent** such as *sodium lauryl sulfate* or *polysorbate 80* may be **appropriate** or even **necessary**.

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- **Processing methods** may also significantly impact *dosage-form performance*.
- **Example:**
  - It **may not be appropriate** to **wet-granulate** *amorphous drug* because water may lower the glass-transition temperature and facilitate recrystallization during or after processing.
  - In other situations, **wet granulation can be used** to avoid potential segregation and CU problems where there is a significant difference in particle size or bulk density between the drug and excipients.

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Topic 2 - Design of Solid Dosage Formulations

Tablet Formulation Design

- Another major consideration: **the anticipated dosage level**.
- In the case of a ***high dose active***, a major proportion of the processing difficulties are traced to the ***physicochemical and mechanical properties of the API***.
- Unfortunately, the key properties of the API may change during scale-up of the synthetic API process, or from lot to lot when outsourced.
- It follows that **continuous monitoring of critical quality attributes (CQAs) of API** that affect the process **is an essential policy**.

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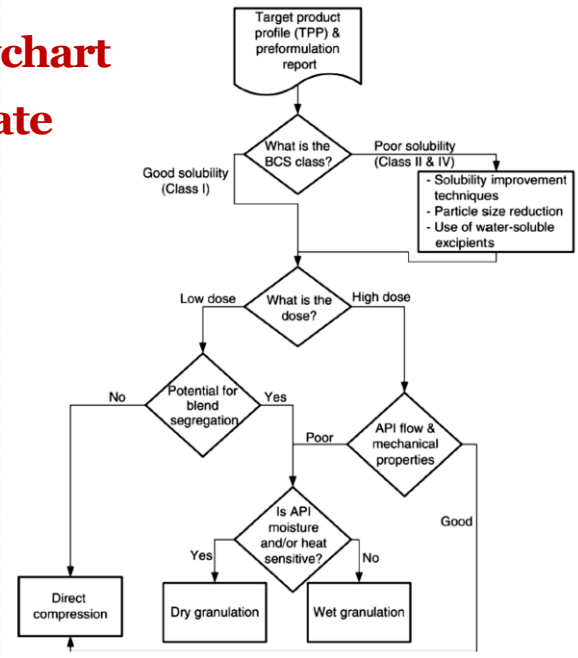
Decision Guiding Flowchart for Selection of Adequate Processing Platform



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Topic 2 - Design of Solid Dosage Formulations

TABLET CHARACTERISTICS

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Tablet Characteristics

- **There are two important classes of tablet characteristics.**
  1. The first set examines the tablet **immediately after manufacturing**;
  2. The second class examines **what happens to the tablet over time**.
- *Immediately after manufacturing and during the formulation process of a tablet*, the **release** of the tablet is of utmost importance.
  - If the tablet does not disintegrate or dissolve in the body, then the efficacious effect desired is likely not going to happen.
  - There are many factors that can affect this from **excipient** choice to **manufacturing**.
- *After manufacturing*, a tablet must maintain **consistency** over time.
  - Similarly to drug release, **excipients** and **processing** can affect the shelf life of a tablet.

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Tablet Characteristics

Release Profile: Factors Affecting In-Vivo Performance

- Release Profile of a tablet can affect in-vivo drug performance, as this is the case it is important to measure this characteristic during development.
- The FDA guidance, ***Dissolution of Immediate Release Solid Oral Dosage Forms***, states the dissolution requirements for an immediate-release drug.
- Dissolution testing is useful in development to determine how processing and formulations can potentially affect in-vivo performance.

What is a dissolution test?

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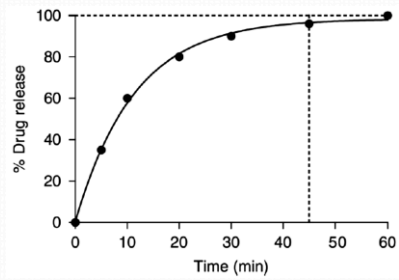
Tablet Characteristics

Release Profile: Factors Affecting In-Vivo Performance

What is a dissolution test?

- Dissolution is a test that provides some assurance of tablet performance by an indication of the mass transfer of the drug into solution.



Typical drug-release profile; very fast initial release with a leveling off.

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Tablet Characteristics

What Affects Dissolution

- There are many things that can affect the dissolution of the tablet:

Processing Conditions

- **Compressing the tablet too hard, overblending the lubricant**

Excipients

- **Amount and choice**

API Physical Properties

Storage

- **Over time, the tablet dissolution may slow down due to excipient interactions with the drug and excipients reaction with each other**

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USING DISSOLUTION TO DETERMINE CQAS

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Using Dissolution to Determine CQAs

Dissolution can help determine

Maximum tablet hardness	Optimal drug substance particle size and/or density	Proper ratio or the amount of excipients

Ratio of Excipients

- A tablet often contains a mixture of water-soluble and -insoluble fillers/binders, and disintegrants that all have the potential to affect the dissolution profile
- Determining the optimal loading of excipients is a difficult task even after the compatible excipients have been chosen

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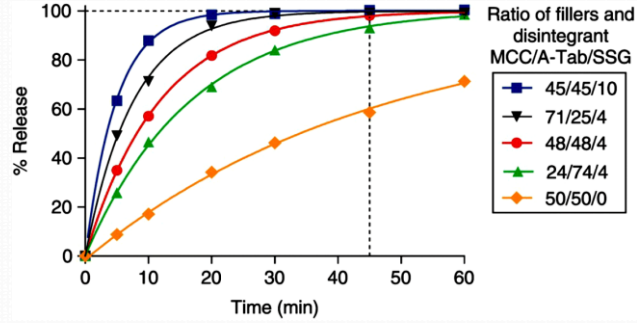
Using Dissolution to Determine CQAs

Ratio of Excipients

- **Example:** compressing a tablet consisting of 20% API with a particle size of 29 µm at a hardness of approximately 10 kP with remaining 80% of the tablet has different ratios of filler, binder, and disintegrant.
  - **Fillers:** Micro Crystalline Cellulose (MCC) and Calcium Di-Basic Phosphate (A-Tab)
  - **Disintegrant:** Sodium Starch Glycolate (SSG)
- It looks like 71/25/4 MCC/A-Tab/SSG has the most optimal performance without putting an excess amount of disintegrant in the tablet.



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Using Dissolution to Determine CQAs

Optimal API Particle Size and Tablet Hardness

- **API particle size** has the potential to affect dissolution based on *different surface area* or *particle morphology*.
- **Tablet hardness** can affect how fast the tablet disintegrates into primary particles enabling the API to dissolve.
- As a rule of thumb about particle size:

There is never an instance where bigger particles will improve the immediate release performance but there are many instances where it will not change the performance.

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Using Dissolution to Determine CQAs

Optimal API Particle Size and Tablet Hardness

- **Example:** Determining the optimal hardness and API particle size-range, dissolution is chosen at the CQA of "not less than (NLT) 70% release at 30 minutes".
- Starting with the "optimal" formulation from the example (71/25/4 MCC/A-Tab/SSG), the material is compressed at five hardness, ranging from approximately 10 to 30 kP, and four different API average particles sizes (d50); 29, 42, 50, and 73 µm.

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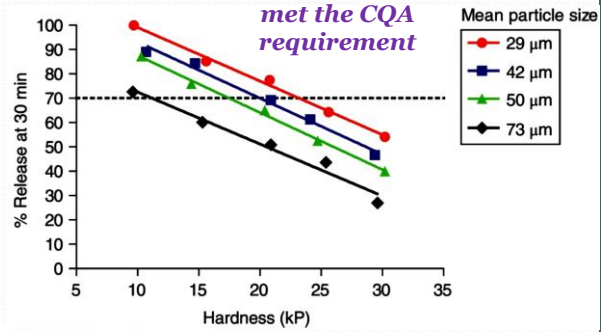
Using Dissolution to Determine CQAs

Optimal API Particle Size and Tablet Hardness

8 of 20 experiments met the CQA requirement



- Based on this information, the relationship between hardness, particle size, and % Release at 30 min is

$$\%R_{at30min} = 139.2 - 0.59 \cdot D50 - 2.25 \cdot hardness$$

- And to maintain the CQA of NLT 70% Release at 30 minutes

$$69.3 \geq 0.59 \cdot D50 + 2.25 \cdot hardness$$

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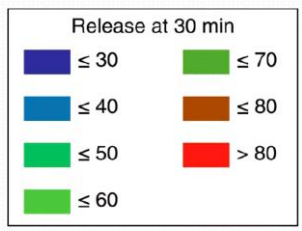
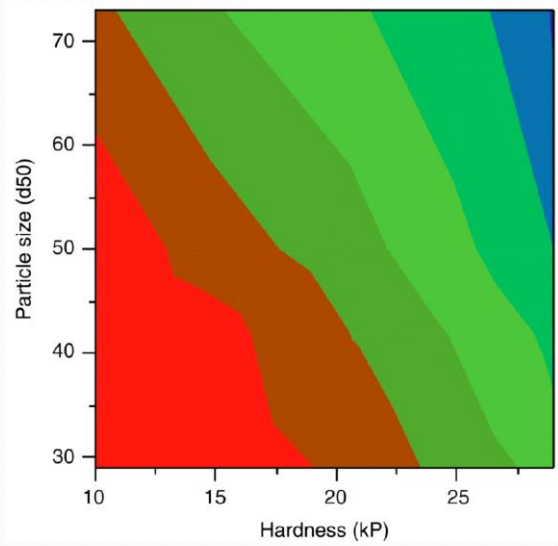
Using Dissolution to Determine CQAs

Optimal API Particle Size and Tablet Hardness

- Contour plot showing dissolution as a function of particle size and hardness.





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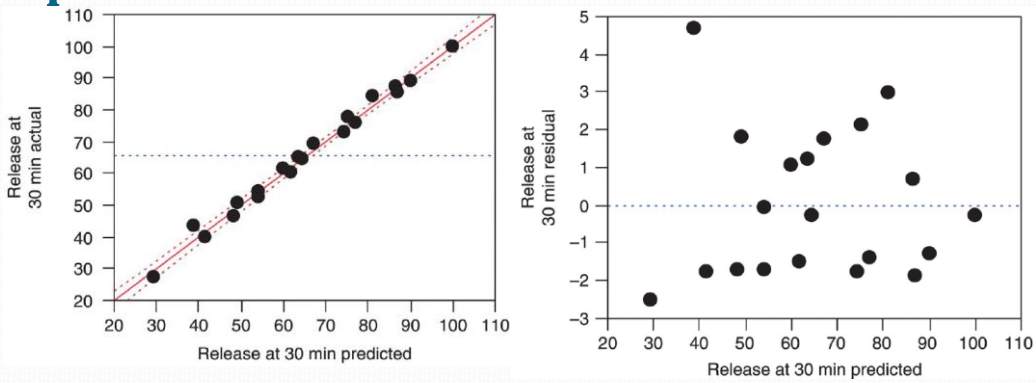
Using Dissolution to Determine CQAs

Optimal API Particle Size and Tablet Hardness



- Last check: Examine the residuals to ensure there is not a systematic error.
  - *The data shown in the figure are randomly distributed, indicating the regression does not have a systematic error.*

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Physical Tablet Characteristics

- Physical attributes of the tablet are important for processing and to ensure a consistent quality drug product is delivered to the customer.

Tablet Hardness	Tablet Thickness	Tablet Friability	Tablet Disintegration	Tablet Weight

- When determining tablet characteristics, consider how the material is to be handled after compression.

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Physical Tablet Characteristics

- **Hardness**
  - Effect
    - Too soft: the tablet can break in storage shipping, coating, packaging.
    - Too hard: the tablet cannot dissolve and may not have the required clinical effect
  - Measurement
    - Hardness tester
    - Typical units: kP, N
- **Friability**
  - Effect
    - Too friable: Tablet cannot withstand further testing
    - Not friable: nothing wrong
  - Measurement
    - Friabilator: 100 revolutions; % weight loss; if capping/lamination occurs

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Physical Tablet Characteristics

- **Thickness**
  - Effect
    - Too thick: May not fit into packaging equipment/package. May not be able to swallow (poor marketing compliance)
    - Too thin: May clog packaging equipment
  - Measurement
    - Caliper
- **Weight**
  - Effect
    - Too heavy: The drug may be overpotent
    - Too light: there may not be enough drug (poor clinical efficacy)
    - Too much variability: may fail content uniformity. Too much yield loss during manufacturing.
  - Measurement
    - Scale

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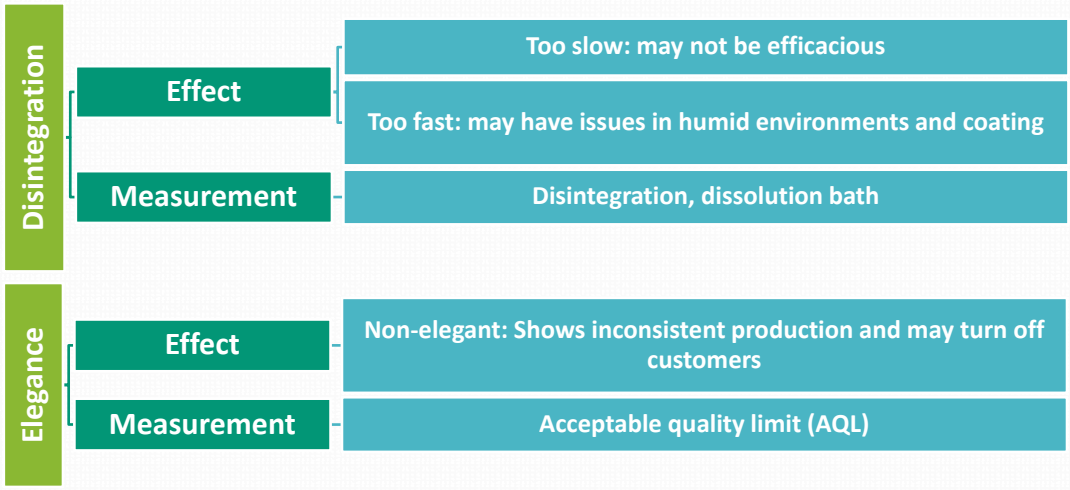
Physical Tablet Characteristics



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